The Journal of Infectious Diseases

MAJOR ARTICLE

Immunogenicity and Safety of an Early Measles Vaccination Schedule at 6 and 12 Months of Age in Human Immunodeficiency Virus (HIV)–Unexposed and HIV-Exposed, Uninfected South African Children

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Background: Measles morbidity and mortality rates are greatest in children <12 months old, with increased susceptibility in human immunodeficiency virus (HIV)–exposed children. We evaluated the immunogenicity and safety of an early 2-dose measles vaccine regimen administered at 6 and 12 months of age in South Africa.

Methods: HIV-unexposed (HU) (n = 212) and HIV-exposed, uninfected (HEU) (n = 71) children received measles vaccination (CAM-70) at 6 and 12 months of age. Measles immunoglobulin G titers were measured by means of enzyme-linked immunosorbent assay before and 1 month after each vaccine dose.

Results: The majority of children (88.2% HU and 95.8% HEU; P = .04) were seronegative (<150 mIU/mL) to measles at 4.2 months of age. This was particularly evident among infants of mothers born from 1992 onwards (year of public nationwide measles vaccine availability). One month after the first measles vaccine, 42.3% of HU and 46.4% of HEU children were seropositive (≥330 mIU/mL). After the second dose, the proportion seropositive increased to 99.0% in HU and 95.3% in HEU children. Safety profiles were similar between HU and HEU children.

Conclusions: Early 2-dose measles vaccination at 6 and 12 months of age was safe and induced antibody responses in HU and HEU children, which could partly offset the early loss of maternally derived antibodies in infants born to predominantly measles-vaccinated mothers.

Clinical Trials Registration: NCT03330171

Keywords. measles vaccine; early dose; safety; immunity; HIV exposure.

Measles virus infection remains an important cause of vaccine-preventable deaths. An estimated 110 000 deaths were attributed to measles globally in 2017, despite an 84% decline in measles mortality between 2000 and 2016 [1, 2]. Measles-associated morbidity and case-fatality rates are highest among children <12 months of age [3–6]. The majority of children are susceptible to measles infection before reaching the age of routine measles immunization [7–10]. In South Africa, during a measles outbreak in 2009–2011, 24% of laboratory-confirmed cases (4284 of 17 530) were identified among children aged <9 months, with age-specific incidences of 302, 1083, 724, and 54 per 100 000 population, respectively, in children aged <6 months, 6–8 months, 8–11 months, and ≥5 years [11].

Measles vaccine (MV) was recommended for inclusion in public immunization programs (PIPs) of low- and middle-income countries during the 1970s and 1980s by the Expanded Programme on Immunization of the World Health Organization (WHO) [12]. Vaccination coverage increased to 73% in the WHO African Region since 2000, according to WHO/UNICEF estimates of national immunization coverage [13]. Consequently, current immunity against measles among women of childbearing age is more likely to be derived by MV during childhood than by immunity acquired through previous natural infection.

Children born to women who derived immunity mainly through vaccination have lower transplacental acquisition of measles antibodies from their mothers [14] and become susceptible to measles as early as 3.3 months of age [15]. Furthermore,

Received 20 May 2019; editorial decision 1 July 2019; accepted 4 July 2019; published online July 6, 2019.

Presented in part: European Society for Paediatric Infectious Diseases Annual Meeting, Ljubljana, Slovenia, 10 May 2019. Abstract number: ESPID19-0249.

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The Journal of Infectious Diseases® 2019;220:1529–38

DOI: 10.1093/infdis/jiz348

children born to human immunodeficiency virus (HIV)–infected women are at heightened risk of measles infection owing to reduced transplacental transfer of measles-specific antibodies [8, 16–19]. The lower concentration of transplacentally acquired antibody, however, may lend itself to earlier measles vaccination in infancy, with immunogenicity less likely to be impeded by interference of maternal-derived antibody [20]. Vaccinating at an earlier age could mitigate serious measles complications during early and middle infancy [21, 22]. Early vaccination at 6 months of age, however, induced lower antibody levels than vaccination at 9 or 12 months [23].

In settings with high incidence of measles and HIV-infection, WHO recommends a supplementary dose of MV from 6 months of age, followed by 2 doses at the recommended ages (usually at 9–12 and 15–18 months) [24]. South Africa introduced MV in the PIP in 1983, but it has only been widely available since 1992 [25]. Until recently MV (Schwarz strain) was administered at 9 and 18 months of age. As of December 2015, South Africa implemented an early 2-dose MV schedule of a CAM-70 strain (Measbio) administered at 6 and 12 months of age [26]. Whereas Schwarz was derived from the Edmonston strain, CAM-70 was developed from a Japanese wild-type isolate [27]. The reasons for lowering the age at vaccination included the high incidence of measles in children aged <9 months during the outbreak in 2009–2011 and regulatory restrictions regarding coadministration of Measbio with other vaccines (personal correspondence, S.A. Madhi, South African National Advisory Group on Immunization, 27 February 2019).

HIV infection in pregnant women in South Africa ranks among the highest in the world, with rates of approximately 30% between 2005 and 2015 [28]. Because of effective prevention of mother-to-child transmission programs, an increasing proportion of South African children born to these mothers are HIV-exposed but uninfected (HEU) [29]. In a recent systematic review, HEU children showed similar serological response when vaccinated at 6 months compared with HIV-unexposed (HU) children, with 68% and 94% being seropositive after the first and second doses, respectively [30].

The limited number of serological studies on early measles vaccination in HEU and HU children in low- and middle-income countries highlights the need to provide evidence for the current South African recommendations. The current study aimed to evaluate the immunogenicity and safety of 2-dose MV regimen administered to HU and HEU children at 6 and 12 months of age.

METHODS

Study Design

This prospective observational cohort study included HU children coenrolled in a randomized, open-label trial evaluating the noninferiority of 2 versus 3 doses of pneumococcal conjugate vaccine (NCT02943902) and a parallel cohort of HEU children (NCT03330171). Children were identified from hospital birth registers, postnatal wards and neighboring primary health clinics and invited for screening at the Respiratory and Meningeal Pathogens Research Unit, based at Chris Hani Baragwanath Academic Hospital, Soweto, South Africa. Healthy children aged 6–18 weeks, ≥37 weeks' gestation at birth and birth weight >2499 g, were eligible for enrollment. Criteria for inclusion, exclusion and classification of HIV status are listed in the Supplementary Data.

Participants were vaccinated under the current South African recommendations, with subcutaneous injection of live attenuated MV (MeasBio; BioFarma) at 6 months (182 ± 14 days) and 12 months (365 ± 14 days) of age. Participants received other childhood vaccines according to the PIP, except for the randomization to different pneumococcal conjugate vaccine schedules in the parent protocol.

Assessment of Outcomes

Venous blood samples were collected from all participants approximately 2 months before the first MV dose (MV1) (age, 4.2 months; mean [standard deviation], 126 [14] days), 1 month after MV1 (age 7 months; 28–35 days after vaccination), before the second MV dose (MV2) (age 12 months; 365 ± 14 days), and 1 month after MV2 (age 13 months; 28–35 days after vaccination). Children were observed after each vaccine injection for 30 minutes. Safety evaluation for solicited adverse events was only included in the protocol as an amendment, resulting in 102 of 278 children (37%) with safety evaluation after MV1 and 260 of 262 (99%) after MV2. Parents were provided with a vaccination report card to report local injection site (pain/tenderness, redness, swelling, and itching) and systemic (fever, vomiting, poor appetite, irritability and decreased activity) symptoms on a daily basis for 7 days after each injection. Adverse events were graded on a 1–3 scale, using symptom-specific definitions outlined in the vaccination report card. Serious adverse events were documented throughout the study.

Laboratory Methods

Blood samples were centrifuged and serum samples stored at −70°C at the Respiratory and Meningeal Pathogens Research Unit laboratory, until testing. Measles immunoglobulin G (IgG) antibody levels were analyzed using a commercial enzyme-linked immunosorbent assay (ELISA) kit (Enzygnost; Dade Behring), according to the manufacturer's instructions. Optical density (OD) values were converted to milli-international units per milliliter using the alpha method with calibration against the first measles antigen WHO international reference preparation [31, 32]. Measles seronegativity was defined as IgG titers <150 mIU/mL (OD, <0.1), equivocal as titers 150–329 mIU/mL (OD, 0.1–0.2), seropositivity as titers ≥330 mIU/mL (OD, >0.2) and seroconversion as the change from seronegative before to seropositive after vaccination. All equivocal samples were

retested. If the result was confirmed, the samples were classified as equivocal, otherwise as positive or negative. Seronegative samples were assigned a titer half the value of the assay's detection limit (ie, 75 mIU/mL).

Statistical Analyses

The sample size was calculated based on a significance level of 5% (2 sided), 80% power, 1:3 ratio of HEU to HU children, and a hypothesized 10% lower seropositivity rate between HEU and HU children after 2 MV doses. The sample size was adjusted upward by 10% to account for loss to follow-up, resulting in a total minimal sample size of 270 participants.

Geometric mean titers (GMTs) of measles antibody concentrations and 95% confidence intervals (CIs) were calculated following natural logarithmic transformation of titer values and were compared between the 2 study groups by means of multivariable linear regression, using the following covariates: sex, race, maternal age, antibody levels before MV1. and age at the serology visit. The proportions of participants meeting the putative thresholds for seronegativity, seropositivity, and seroconversion were compared by means of multivariable logistic regression, adjusting for the above-mentioned covariates. The association between maternal age in years or classified as maternal year of birth before 1992 (the year of wide public MV availability) or 1992 and beyond, and the proportions of seronegative and seropositive children at the pre-MV1 visit were explored using logistic regression, adjusting for HIV exposure.

Pre- and post-MV GMTs were correlated using Spearman correlation, and the association between proportions seronegative before and after MV were evaluated using (exact) logistic regression. Safety analysis included the proportion of children with ≥1 event (including solicited local and systemic reactions and serious adverse events) and the proportion with solicited grade 3 events. Differences were considered significant at $P < .05$. Analysis was by modified intention to treat, with all participants included if antibody results were available. A per-protocol analysis was performed including only those children who were vaccinated or had blood samples collected within the protocol-defined time periods. Stata13 (StataCorp) and R (version 3.5.1) software were used.

Ethics

The study protocol was approved by the Human Research Ethics Committee of the University of the Witwatersrand, South Africa (the Human Research Ethics Committee reference number: M170276). Parents provided written informed consent before study entry.

RESULTS

From April to October 2017, a total of 283 children were enrolled in the study, including 212 HU (75%) and 71 HEU (25%) (Figure 1). Baseline characteristics at study initiation did not differ between HU and HEU children, except that mothers of HEU children were older (30.7 vs 27.9 years for HU children) (Supplementary Table 1). The baseline characteristics of HU children who consented to the measles study did not differ significantly from those of children who were enrolled only in the main parent study (data not shown). Overall, the mean (standard deviation) age at was 4.2 (0.2) months at the pre-MV1 serology visit, 6.0 (0.1) months at the MV1 visit, 7.0 (0.1) months at the post-MV1 serology visit, 12.0 (0.2) months at the MV2 visit, and 13.0 (0.2) months at the post-MV2 serology visit. HU children were slightly younger than HEU children at the vaccination and serology visits (difference, −0.1 month) (Supplementary Table 1).

Measles Antibodies Titers

In analyses adjusted for sex, race, maternal age, antibody levels before MV1 (only for subsequent time points), and age at serology, HU children had higher GMTs than HEU children before MV1 (93 [95% CI, 85–102] vs 82 [74–91] mIU/mL, respectively; $P = .02$). GMTs were similar between HU and HEU children after MV1 (223 [95% CI, 191–260] vs 251 [197–319] mIU/mL, respectively) and after MV2 (2751 [2402–3152] vs 3226 [2429–4286] mIU/mL). Before MV2, however, GMTs were lower in HU than in HEU children (233 [95% CI, 196–277] vs 340 [249–464] mIU/mL; $P = .04$) (Figure 2*A* and Table 1).

At the pre-MV1 visit (mean age, 4.2 months), more HEU than HU children were seronegative (titers <150 mIU/mL, 95.8% vs 88.2%, respectively; $P = .02$), and only 4.2% and 6.6%, respectively, were seropositive (≥330 mIU/mL) (Figure 2*B* and Table 1). One month after MV1, the percentage of seronegative children was nonsignificantly higher in HU (44.7%) than in HEU (34.8%) children, but the percentages who were seropositive (42.3% and 46.4%, respectively) or had seroconverted (48.1% and 50.0%) were similar between groups.

Five months later, before MV2 at age 12 months, 42.8% of HU and 54.1% of HEU children were seropositive ($P = .34$), whereas 46.8% and 29.5%, respectively, were seronegative ($P = .03$). The percentage of seropositive children increased to 99.0% in HU and 95.3% in HEU children 1 month after MV2; and only 1.0% and 1.6%, respectively, remained seronegative (Figure 2*B* and Table 1). After MV2, seroconversion rates from before MV2 were higher in HU (97.9%) than in HEU (83.3%) children ($P = .01$).

Per-protocol analysis, excluding children who were vaccinated or had blood samples collected outside the protocol-defined time periods, yielded similar results, except that differences between HU and HEU in pre-MV2 GMTs became marginally significant ($P = .055$) (Supplementary Table 2).

At 4.2 months of age (before MV1), maternal age was inversely associated with the percentage of seronegative children (adjusted odds ratio [aOR], 0.88; 95% CI, .82–.94; $P < .001$) and positively associated with percentage of seropositive children

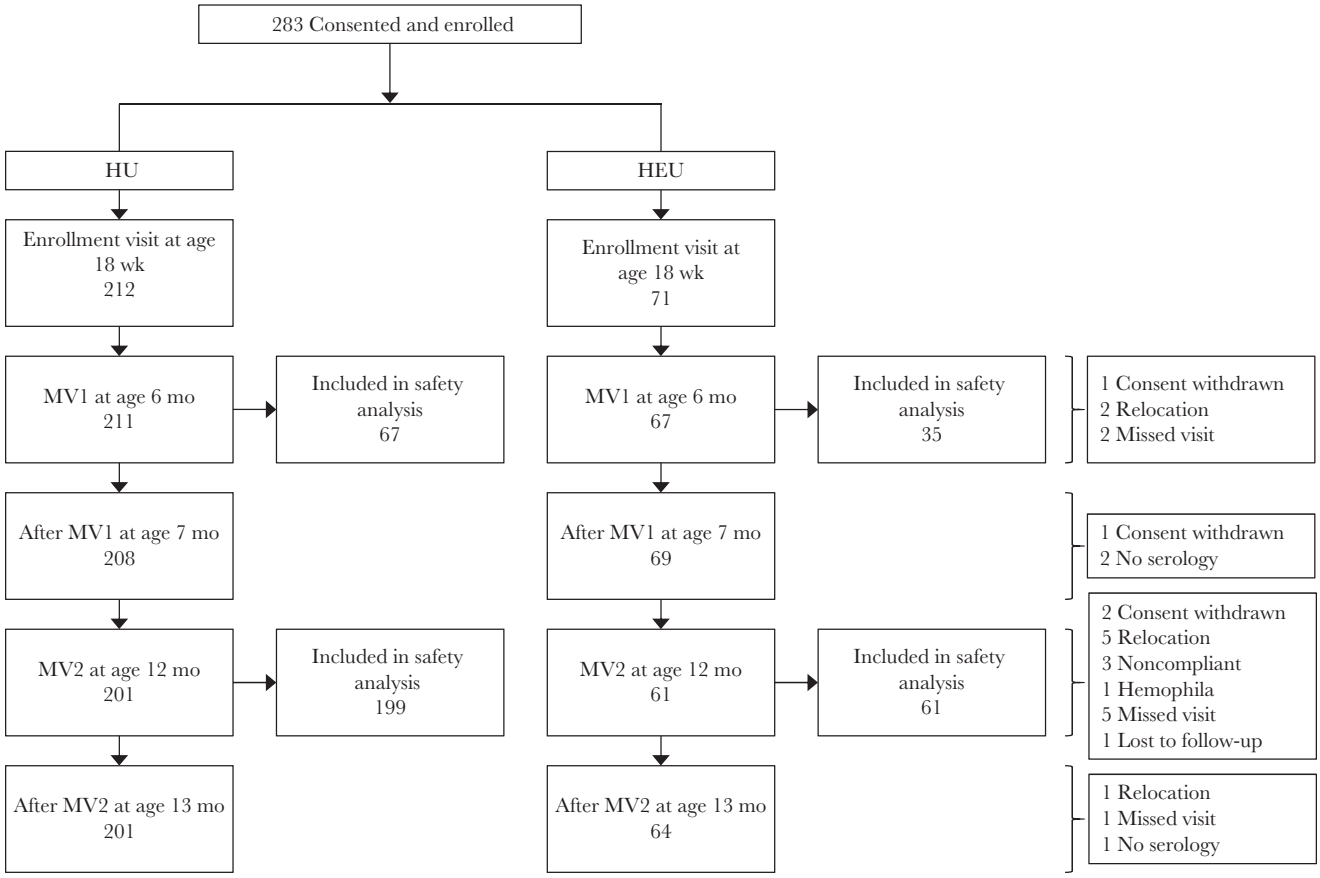

Figure 1. Flow diagram of study participants. One human immunodeficiency virus (HIV)–exposed, uninfected (HEU) and 1 HIV-unexposed (HU) child missed a visit at time of the first measles vaccine dose (MV1) and were vaccinated at the local clinic. Safety analysis was completed in a subset of participants at MV1, owing to diary card introduction during the course of the study. Four HEU and 1 HU child missed a visit at time of the second measles vaccination (MV2) and were vaccinated at the local clinic, and 1 HU child missed the serology visit after MV2.

(1.17; 1.07–1.27; $P < .001$) (Table 2). Before vaccination, 0% of infants (0 of 91) with mothers born since 1992 were seropositive, compared with 8.9% (17 of 192) with mothers born before 1992. Furthermore, a positive association was observed between year of maternal birth category and the percentage of seronegative children (aOR, 5.01; 95% CI, 1.46–17.17; $P = .01$), with adjustment for HIV exposure (Table 2).

There was a negative correlation between pre- and post-MV1 GMTs (Spearman correlation coefficient, −0.27; $P < .001$) (Supplementary Figure 1*A*). Similarly, children with undetectable antibody levels before vaccination were more likely to have titers ≥150 mIU/mL (aOR, 9.67; 95% CI, 3.25–28.84; $P < .001$) or to be seropositive after MV1 (11.63; 2.70–50.20; $P = .001$). A positive correlation was found between pre- and post-MV2 GMTs (Spearman correlation coefficient, 0.50; $P < .001$) (Supplementary Figure 1*B*).

Safety

The frequency and severity of solicited local and systemic reactions during the 7 days after each measles vaccination were similar in HU and HEU children (Table 3). Most children showed no solicited reactions. After MV1, no grade 3 local injection site reactions occurred; 9% (6 of 67) HU and no HEU children experienced grade 3 systemic reactions. After MV2, grade 3 local reactions were recorded in 1% (2 of 199) HU and 5% (3 of 61) HEU children; and grade 3 systemic adverse events in 9% (17 of 199) HU and 10% (6 of 61) HEU children. The most common local reactions were pain or tenderness and redness. Common systemic adverse events were decreased appetite and irritability in HU and decreased appetite and decreased activity in HEU children (Supplementary Table 3). The proportion with pain or tenderness after MV1 was higher in HEU children (mild pain or tenderness in 23%, moderate in 6%) than in HU children (mild in 16%) ($P = .006$).

Thirty serious adverse events occurred throughout the study, 2 in HU children within 28 days after measles injection (Table 3). One child had bronchopneumonia and otitis media with onset 9 days after MV1, and another had bronchiolitis and otitis media with onset 20 days after MV2 (Supplementary Table 4). All serious adverse events had mild or moderate severity, and none were classified as MV related. No deaths occurred. None of the HIV-exposed children became HIV positive during the study period.

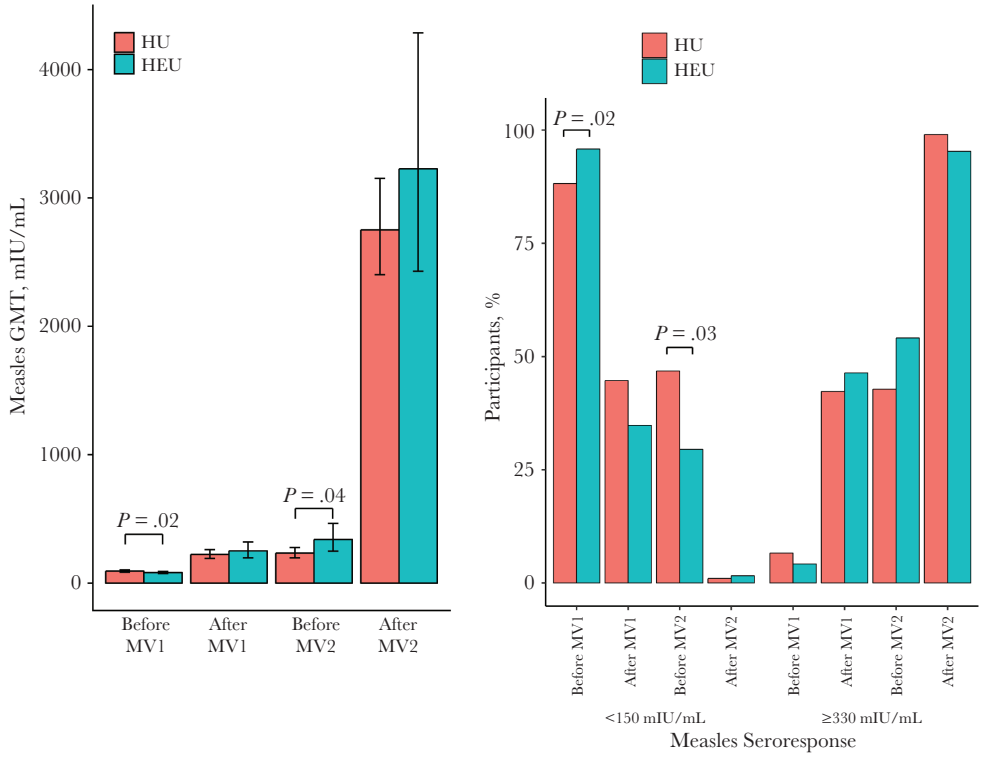

Figure 2. *A,* Measles antibody geometric mean titers (GMTs) in human immunodeficiency virus (HIV)–exposed, uninfected and HIV-unexposed (HU) children, before and after first and second measles vaccine dose (MV1 and MV2) *B,* Proportions of seronegative and seropositive children before and after MV1 and MV2. *P* values were calculated by means of either linear or logistic regression, with adjustment for sex, race, maternal age, measles antibody levels before MV1, and age at serology.

DISCUSSION

The results of this prospective cohort study showed that an early 2-dose measles vaccination schedule administered at 6 and 12 months of age is similarly safe and immunogenic in HU and HEU children. The vast majority (90.1%) of children aged 4.2 months in our study were seronegative for measles antibody. This was especially evident among infants of women born since 1992 (when measles vaccination became widely available in the South African PIP). These findings underscore the importance of reconsidering measles dosing schedules in settings similar to ours.

Administration of 2 doses of MV at 6 and 12 months of age resulted in seropositivity rates of 99.0% and 95.3% in HU and HEU children, respectively, 1 month after MV2. Our results corroborate findings from other studies on early measles vaccination regimens in Africa [33–37] and a Brazilian study from 1990 that examined the humoral response to a CAM-70 strain containing MV administered at 6 and 11 months of age, reporting 89% seroconversion rates by immunofluorescence assay and 97% by ELISA after the second dose [38]. However, the rise in antibody levels induced by a second vaccination may be short-lived, and titers could fall back to preboost levels [39]. A recent study reported a decrease in long-term concentration and avidity of measles virus-specific neutralizing antibodies after early vaccination compared with vaccination at a later age [40]. Hence, durability of the response to early vaccination needs to established, to rule out future vaccine failures and to prevent reductions in maternal antibody transfer in future generations.

A high proportion of children had antibody levels below the assay detection limit at 4.2 months of age, similar to findings of an earlier study from our setting [41]. Even in areas that have eliminated measles, a number of children may be susceptible to infection before receiving MV1 if given at age 12 months [10, 14, 42]. The increase in measles seronegativity among young children has been attributed in part to lower levels of transplacental IgG transfer to the fetus in women who derived antibody from measles vaccination rather than after natural viral infection [20]. In our study, measles antibody seronegativity in infants before measles vaccination (4.2 months of age), was associated with younger maternal age and women born after wide implementation of MV into the South African PIP. Even lower concentrations of measles-specific antibody have been detected in children born to HIV-infected women compared with HU children [8, 16–19], as corroborated by our findings of 95.8% seronegativity in HEU compared with 88.2% in HU children before measles immunization. A previous study from our setting on cord blood samples collected in 2007 from mother-newborn dyads reported measles seronegativity prevalence of 5.6% in HU (6 of 107) and 8.7% of HEU (17 of

Table 1. Measles Antibody Geometric Mean Titers and Proportions of Seropositive and Seronegative Children Before and After Both Measles Vaccines

Serological Status Before and After MV1 and MV2	Children, No. (%)[a]		
	HU	HEU	Total
Before MV1	n = 212	n = 71	n = 283
Measles antibody, GMT (95% CI)	93 (85–102)[b]	82 (74–91)[b]	90.0 (84–97)
Seronegative (IgG titer <150 mIU/mL)	187 (88.2)[b]	68 (95.8)[b]	255 (90.1)
Seropositive (IgG titer ≥330 mIU/mL)	14 (6.6)	3 (4.2)	17 (6.0)
After MV1	n = 208	n = 69	n = 277
GMT (95% CI)	223 (191–260)	251 (197–319)	230 (202–261)
Seronegative	93 (44.7)	24 (34.8)	117 (42.2)
Seropositive	88 (42.3)	32 (46.4)	120 (43.3)
Seroconversion[c]	90 (48.1)	34 (50.0)	124 (48.6)
Before MV2	n = 201	n = 61	n = 262
GMT (95% CI)	233 (196–277)[d]	340 (249–464)[d]	254 (218–296)
Seronegative	94 (46.8)[e]	18 (29.5)[e]	112 (42.8)
Seropositive	86 (42.8)	33 (54.1)	119 (45.4)
After MV2	n = 200	n = 64	n = 264
GMT (95% CI)	2751 (2402–3152)	3226 (2429–4286)	2860 (2528–3235)
Seronegative	2 (1.0)	1 (1.6)	3 (1.1)
Seropositive	198 (99.0)	61 (95.3)	259 (98.1)
Seroconversion[f]	92 (97.9)[g]	15 (83.3)[g]	107 (95.5)

Abbreviations: CI, confidence interval; GMT, geometric mean titer; HEU, human immunodeficiency virus (HIV)–exposed, uninfected; HU, HIV-unexposed; IgG, immunoglobulin G; MV1, first measles vaccine dose; MV2, second measles vaccine dose.

[a]Data represent no. (%) of children unless otherwise specified.

[b]$P = .02$. (P values were calculated by means of either linear or logistic regression and adjusted for sex, race, maternal age, measles antibody levels before MV1, and age at serology.)

[c]A total of 255 children had titers <150 mIU/mL before MV1 (187 HU and 68 HEU children). Seroconversion was defined as a change from titers ≤150 mIU/mL before to ≥330 mIU/mL after vaccination.

[d]$P = .04$.

[e]$P = .03$.

[f]A total of 112 children had titers <150 mIU/mL before MV2 (94 HU and 18 HEU children).

[g]$P = .01$.

196) children [8]. This indicates rapid waning of measles antibodies in the first 4 months after birth, thereby creating a group of infants susceptible to measles at a younger age.

We found that 55.3% of HU and 65.2% of HEU children had titers ≥150 mIU/mL after a single MV dose at age 6 months, findings in line with those of a Malawian study on early measles vaccination in which 62% of HU and 68% of HEU children had titers ≥120 mIU/mL (as measured by enzyme immunoassay) after 1 dose of MV [33, 34]. Our rates, however, are lower than the 77% seroprotected (≥125 mIU/mL, as measured by measles hemagglutination inhibition test) reported from Guinea-Bissau [35] and lower than the overall pooled estimate for seropositivity after MV at 6 months (75%; 95% CI, 68%–82%) [43]. The seroconversion rate at age 6 months (48.6%), which may depend on the vaccine strain, was also lower than that reported in a meta-analysis evaluating MV at 6 months (76%; 95% CI, 71%–82%) [43]. Our seropositivity rates after vaccination at age 6 months are similarly lower compared with findings from our setting when vaccination was done at age 9 months, with 91.1% of HU and 94.8% of HEU children seropositive (≥330 mIU/mL, as measured by ELISA) 6.6 months after MV1 [41]. Our results suggest that a single early dose of MV is only partially effective

Table 2. Association of Maternal Age With Percentage of Seronegative and Seropositive Children Before the First Measles Dose

Characteristic	Nonseronegative (n = 28)	Seronegative[a] (n = 255)	Adjusted OR (95% CI) for Seronegativity[b]	*P* Value	Nonseropositive (n = 266)	Seropositive[c] (n = 17)	Adjusted OR (95% CI) for Seroprotection[b]	*P* Value
Maternal age, mean (SD), y	32.3 (5.3)	28.2 (6.1)	.88 (.82–.94)	<.001	28.3 (6.1)	33.6 (4.3)	1.17 (1.07–1.27)	<.001
Maternal year of birth, no. (%)								
Before 1992	25 (89)	167 (65)	Reference	.01	175 (66)	17 (100)	…	…
1992 or later	3 (11)	88 (35)	5.01 (1.46–17.17)		91 (34)	0 (0)	NA	NA

Abbreviations: CI, confidence interval; NA, not applicable; OR, odds ratio.

[a]Seronegativity was defined as an immunoglobulin G titer <150 mIU/mL.

[b]ORs were adjusted for human immunodeficiency virus exposure.

[c]Seropositivity was defined as an immunoglobulin G titer ≥330 mIU/mL.

Table 3. Reported Adverse Events After Immunization With Measles Vaccine at 6 and 12 Months of Age, by Human Immunodeficiency Virus Exposure

Adverse Events	Children With Reaction/Total,[a] No. (%)	
	HIV Unexposed	HIV Exposed, Uninfected
Solicited reactions during 1st 7 d after MV1		
Local reactions		
Any	17/67 (25)	12/35 (34)
Severe	0/67 (0)	0/35 (0)
Systemic reactions		
Any	36/67 (54)	15/35 (43)
Severe	6/67 (9)	0/35 (0)
Solicited reactions during 1st 7 d after MV2		
Local reactions		
Any	49/199 (25)	14/61 (23)
Severe	2/199 (1)	3/61 (5)
Systemic reactions		
Any	106/199 (53)	27/61 (44)
Severe	17/199 (9)	6/61 (10)
Unsolicited serious adverse event after measles vaccination[b]		
≤28 d after injection	2/211 (1)	0/67 (0)
Throughout the study period	24/211 (11)	6/67 (9)
Per study participant	20/211 (9)	4/67 (6)
Related to measles vaccination	0/211 (0)	0//67 (0)

Abbreviations: HIV, human immunodeficiency virus; MV1, first measles vaccine dose; MV2, second measles vaccine dose.

[a]Total number with vaccination report card/serious adverse event assessment.

[b]Some participants had >1 serious adverse event. Serious adverse events are reported in Results and in Supplementary Table 5.

in inducing humoral immune responses and that administration of the second dose remains essential.

When evaluating the effect of maternal HIV infection on infant vaccine-induced measles antibody responses, we observed that HEU children, compared with HU children, had similar or higher post-MV1 GMTs, and similar proportions had titers ≥330 mIU/mL. Previous studies on responses to primary vaccination have reported similar findings [19, 41, 44]. This may be explained by the association between prevaccination antibody levels in HEU children and a heightened humoral immune response to childhood vaccines, owing to reduced interference of maternally acquired antibody [19]. Similarly, our study found prevaccination antibody concentrations to be lower in HEU than in HU children. In addition, we found that children who were seronegative before vaccination were more likely to have titers ≥150 mIU/mL or to be seropositive after MV1.

We observed an increase in antibody titers between post-MV1 and pre-MV2 study visits. This could be explained by subclinical exposure to wild-type measles virus and avidity maturation. During 2017, a localized measles outbreak occurred in the Gauteng province in South Africa, with a total of 96 laboratory-confirmed cases [45]. The measles cases were not detected in Soweto, the area where most study participants resided. In response to the outbreak, a province-wide supplemental vaccination campaign was conducted from May to June 2017 [45]. However, only 1 study participant was reported to have received additional measles vaccination. No participant had clinical measles infection during the study.

The current study examined the safety of CAM-70 measles virus vaccine given at 6 months of age. Prior studies have demonstrated the safety of other MV strains when administered before 9 months of age [46–48]. The WHO states that internationally qualified attenuated MV may be used interchangeably within immunization programs and considers them to be safe and effective [24], but strain-dependent differences in immunogenicity have been described [49]. We report that an early 2-dose MV regimen is safe and well tolerated. The frequencies of local and systemic adverse events were comparable to those in previous studies [24, 30, 46]. Grade 3 solicited systemic reactions were reported more often than in a previous study that coadministered a fully liquid hexavalent vaccine and a measles-mumps-rubella and varicella vaccine at age 15–18 months in healthy South African children [50].

A limitation of our study was the late introduction of vaccination report cards; as a result, only 37% of participants were included in the safety analysis after MV1. Furthermore, solicited adverse events were followed up until day 7 after vaccination, thereby excluding adverse events occurring during the second week after MV. Furthermore, we did not assess antibody titers for more than 1 month after MV2. Long-term follow-up of study participants is currently ongoing. Another limitation is the use of an ELISA instead of the reference-standard

plaque reduction neutralization test, especially because ELISA has reduced sensitivity at low antibody levels and may therefore underestimate humoral immunity. As a result, currently undetectable maternal antibodies by ELISA could be detected by plaque reduction neutralization test and may interfere with vaccination response.

In conclusion, early 2-dose measles vaccination at age 6 and 12 months with the CAM-70 strain is immunogenic and induces similar post-MV2 responses in HU and HEU children. A window of vulnerability exists before 6 months of age, as well as between 6 and 12 months of age. This is particularly important, because an increased number of mothers will have vaccine-derived instead of naturally acquired immunity, which is associated with early loss of maternal antibodies. When combined with a reduction in measles vaccination coverage, outbreaks can occur, affecting those most susceptible (ie, young infants). Earlier vaccination could narrow the vulnerability gap, suggesting the need for new MVs that are more immunogenic in younger age groups, possibly as young as 3–4 months in settings with high HIV incidence. In addition, future studies should optimize vaccination dosing schedules and evaluate the sustainability of protection with an accelerated measles vaccination schedule.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Acknowledgments. We thank the participants and their parents, study nurses, research assistants, and laboratory technicians for their help in recruitment, vaccination, and follow-up of participants.

Author contributions. All authors contributed significantly. E. A. M. L. M., M. C. N., D. E. G., K. K. G., and S. A. M. provided input for writing of the manuscript; E. A. M. L. M., M. C. N., W. B., C. L. C., and S. A. M. designed the study; S. B., B. T. I., W. B., L. J., and A. K. were responsible for clinical aspects of the study; A. M. was responsible for laboratory management; E. A. M. L. M. analyzed the samples in the laboratory and wrote the first draft of the manuscript, and all authors contributed to subsequent drafts. All authors read and approved the final version of the manuscript.

Financial support. This work was supported by The Biologicals and Vaccines Institute of Southern Africa (Biovac), the Department of Science and Technology, Republic of South Africa (DST/CON 0133/2012)/National Research Foundation (8527787849). The parent trial was funded by the Bill & Melinda Gates Foundation (grant OPP1152352).

Potential conflicts of interest. E. A. M. L. M., M. C. N., S. B., B. T. I., W. B., L. J., A. K., A. M., C. L. C., and S. A. M. report grants from The Biologicals and Vaccines Institute of Southern Africa (Biovac), during the conduct of the study. C. L. C. reports grants from the Bill & Melinda Gates Foundation and the Immunising Pregnant Women and Infants Network (IMPRINT) and grants and personal fees from Pfizer, grants outside the submitted work. S. A. M. reports grants and personal fees from the Bill & Melinda Gates Foundation and grants from Pfizer, GlaxoSmithKline, Minervax, and Sanofi Pasteur, outside the submitted work. M. C. N. reports grants from the Bill & Melinda Gates Foundation and MedImmune and personal fees from Sanofi Pasteur and Pfizer, outside the submitted work. All other authors: No reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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